

Applicants: William C. Olson and Paul J. Maddon
Serial No.: 10/681,879
Filed: October 9, 2003
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REMARKS

Claims 1, 10-13, 42-45 and 47-52 are pending in the subject application. By this Amendment, applicants have amended claims 1, 42 and 44, and have canceled and 49-52 without prejudice or disclaimer. Support for amended claims 1, 42, and 44 may be found in the specification *inter alia* at page 14, lines 24-29. Applicants maintain that amended claims 1, 42 and 44 do not raise any issue of new matter and request that this Amendment be entered. Accordingly, upon entry of this Amendment, claims 1, 10-13, 42-45, 47 and 48 will be pending and under examination.

Rejections under 35 U.S.C. §103(a)

1. Allaway et al. in view of Bolognesi et al.

The Examiner rejected claims 1, 10-13, 42-45 and 47-50 under 35 U.S.C. §103(a) as allegedly unpatentable over Allaway et al. (5,817,767; 'Allaway') in view of Bolognesi et al. (5,464,933; 'Bolognesi').

Specifically, the Examiner stated that Allaway discloses compositions comprising CD4-based immunoconjugates and antibodies against gp120 or gp41 in a ratio of between about 0.1 and about 100. The Examiner further stated that although Allaway et al. do not disclose T-20, Bolognesi discloses DP-178, i.e. T-20. The Examiner alleged that one skilled in the art would have been motivated to use the peptide of Bolognesi in Allaway's method.

In response, applicants respectfully traverse the Examiner's ground of rejection.

Applicants' invention as recited in the currently amended claims set forth above provides methods which utilize two peptidyl compounds, wherein one compound is a monoclonal antibody or a portion thereof which binds to an epitope of CD4 on the surface of a CD4+ cell and retards attachment of HIV-1 to a CD4+ cell by retarding binding of HIV-1 gp120 envelope glycoprotein to CD4 on the surface of the CD4+ cell and the other peptidyl compound is a peptide designated T-20 (SEQ ID NO:1) which retards gp41 from adopting a conformation capable of

mediating fusion of HIV-1 to a CD4+ cell by binding noncovalently to an epitope on a gp41 fusion intermediate, wherein the relative mass ratio of the compounds ranges from about 100:1 to about 1:100, including the use of compositions comprising an admixture of such two compounds and such compositions.

Allaway discloses the use of two peptidyl compounds to inhibit HIV-1 infection. As the Examiner stated on page 3 of the September 28, 2007 Office Action, Allaway discloses CD4-based immuno-conjugates and antibodies specific for gp120 or gp41. Applicants maintain that none of the compounds disclosed by Allaway binds to an epitope of CD4 on the surface of a cell, including any such antibody or portion thereof as now recited in amended claims 1, 42 and 44. Applicants maintain that Bolognesi also fails to teach any such antibody or portion thereof. Accordingly, applicants maintain that Allaway and Bolognesi in combination do not disclose applicants' now-claimed invention. Accordingly, applicants' maintain that the Examiner has not established a *prima facie* case of obviousness over Allaway and Bolognesi for the subject matter now recited in amended claims 1, 42, and 44, and claims dependent therefrom.

In view of the remarks above, applicants maintain that claims 1, 42 and 44, as now amended, and claims dependent therefrom are not obvious over the combination of Allaway and Bolognesi. Therefore, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection under 35 U.S.C. §103 of claims 1, 10-13, 42 and 44-48.

2. Wang in view of Bolognesi

The Examiner rejected claims 51 and 52 under 35 U.S.C. §103(a) as allegedly obvious over Wang (US 5,961,976) in view of Bolognesi. Specifically, the Examiner stated that claims 51 and 52 require that the monoclonal antibody or portion thereof bind to CD4 of a CD4+ cell and thus retard attachment of gp120 to CD4. The Examiner stated that Wang discloses monoclonal antibodies and fragments thereof which bind to CD4 and retard attachment of gp120 to surface CD4. The Examiner further stated that Wang also discloses methods of administering the antibodies to a subject in combination with other therapeutics for the

treatment of HIV infection, but does not disclose the use of T-20 in combination with the anti-CD4 antibodies. The Examiner also stated that Bolognesi discloses DP-178, i.e. T-20. The Examiner stated that it would have been obvious to one skilled in the art to combine the anti-CD4 antibody and the T-20 peptide into a combination therapy composition and method of treatment. The Examiner further stated that it would have been routine for one skilled in the art to determine the ratio of compounds that would exhibit the desired effect.

In response, applicants note that claims 51 and 52 have been canceled and address this ground of rejection as it may apply to claims 1, 42 and 44 as now amended.

Applicants maintain that although Wang suggests that anti-CD4 antibodies may be administered in combination with other anti-HIV agents, Wang does not disclose any such anti-HIV agents which bind to gp41. In contrast, T-20 binds to the fusion intermediate of gp41. Applicants maintain that it would not have been obvious to one skilled in the art to substitute the peptide of Bolognesi, i.e. T-20, for the anti-viral agent of Wang. Applicants maintain that one skilled in the art could not envisage from the combined teachings of Wang and Bolognesi whether the combination of an anti-CD4 antibody and an anti-viral agent which binds to a gp41 fusion intermediate of HIV-1 would inhibit HIV-1 infection at all, since the two compounds employ different mechanisms for blocking fusion. One skilled in the art would not know whether these two compounds would compete with one another, rather than work together, and would certainly not know that such a combination would work together synergistically when compared to the inhibitory effects of these two compounds individually.

Applicants maintain that neither Wang nor Bolognesi teach or suggest that any combination of two anti-HIV compounds would exhibit any synergistic properties. In contrast, applicants' specification discloses such synergistic effect. As shown in Figures 1-3 of the subject application, the combined effect of the two compounds is greater than an additive effect. As detailed in the specification at page 26, lines 8-10, the degree of synergy was quantified using the Combination Index (CI) method, wherein a CI value greater than 1

indicates antagonism, a CI equal to 1 indicates a purely additive effect, and CI less than 1 indicates a synergistic effect. As shown in Figure 2, potent synergies over broad ranges of inhibitor ratios and concentrations were observed with CI values as low as 0.20 under optimal conditions. These observed synergies translated into 17-fold and 5-fold reductions in the amounts of monoclonal antibody and T-20, respectively, needed to achieve 95% inhibition of viral entry, and even greater dose reductions were observed at higher levels of inhibition (see Figure 3).

As described in the specification at page 27, lines 4-12, HIV-1 attachment and formation of gp41 fusion intermediates are inter-dependent steps. Therefore, HIV-1 attachment inhibitors administered in reduced amount (as shown in Figure 3) retard the binding of gp120 to CD4 but do not inhibit it completely. As a result, gp41 fusion intermediates are formed and persist for longer periods of time at levels below those required for membrane fusion and provide targets for inhibitory agents such as T-20. Accordingly, applicants maintain that any monoclonal antibody which retards HIV-1 attachment, i.e. anti-CD4 monoclonal antibodies, but permits production of gp41 fusion intermediates, will exhibit this synergistic effect.

Applicants maintain that the observed synergy between the two anti-HIV-1 compounds was surprising and unexpected. Thus, applicants maintain that this unexpected synergistic effect renders the claimed invention unobvious over Wang in combination with Bolognesi.

Rejection Under Obviousness-Type Double Patenting

The Examiner maintained the rejection of claims 1, 10-13, 42-45 and 47-52 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-15 of U.S. Patent No. 6,692,745 B2 for reasons of record. As the Examiner has noted, applicants have indicated they might consider filing a terminal disclaimer later in prosecution if allowable claims are indicated and the rejection is applicable thereto.

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Conclusion

In view of the remarks above, applicants maintain that the pending claims are not obvious over either combination of Allaway and Bolognesi, or Wang and Bolognesi and respectfully request that the Examiner reconsider and withdraw the ground of rejection under 35 U.S.C. §103. Applicants respectfully request allowance of all claims pending in the subject application.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

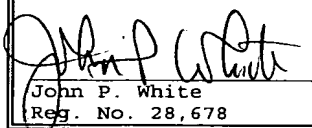
No fee, other than the \$525.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



John P. White
Registration No. 28,678
Attorney for Applicants
Cooper & Dunham, LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited on this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.



John P. White
Reg. No. 28,678

3/25/08
Date